UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/919,298	07/31/2001	Joseph Edward Zahner	16850-8184	2484

32809 7590 06/17/2003

NUCLEUS REMODELING, INC.
3646 DOVER PLACE
ST. LOUIS, MO 63116

EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/17/2003

16

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary	Application No. 09/919,298	Applicant(s) Zahner et al.
	Examiner Joseph Woitach	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 1, 2003*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3-5, 8, and 21-33* is/are pending in the application.

4a) Of the above, claim(s) *23-33* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3-5, 8, 21, and 22* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This application filed July 31, 2001, claims benefit to provisional application 60/254,551, filed December 12, 2000.

Applicants' amendment filed April 1, 2003, paper number 15, has been received and entered. Claims 2, 6, 7 and 9 have been canceled. Claims 1, 3 and 4 have been amended. Claims 21-33 have been added. Claims 1, 3-5, 8 and 21-33 are pending.

Election/Restriction

Applicant's election in Paper No. 13 without traverse of Group I as drawn to a method of producing pluripotent stem cells from adult somatic cells (see restriction requirement mailed October 15, 2002, paper number 12, page 2) was acknowledged. Newly added claims 21 and 22 dependent on claim 1, and will be examined with the elected invention.

Newly submitted claims 23-33 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: newly added independent claim 23 is drawn to specifically reprogramming a keratinocyte into a cell which expresses a neurofilament, cardiac actin or alpha-antitrypsin. A keratinocyte is a somatic cell, however the specific markers expressed by the resulting cell are not markers of pluripotent stem cells. Newly added claims 23-33 are directed to specifically altering a keratinocyte to provide a cell with a different phenotype as defined by the expression of specific genes, not methods of producing

pluripotent stem cells from adult somatic cells. Because the resulting cell is not a pluripotent stem cell, the newly added claims would not be interpreted to be encompassed by the elected invention. In the instant case, specifically defining the starting somatic cell would not be interpreted as a narrowing embodiment of the elected invention because the resulting cell is not a pluripotent stem cell. Thus, the method encompassed by claim 23 and dependent claims 24-33 encompasses a method which is different from that elected.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 23-33 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1, 3-5, 8 and 21-33 are pending. Claims 23-33 are withdrawn from consideration as being directed to a non-elected invention under 37 CFR 1,142(b). Claims 1, 3-5, 8, 21 and 22 are currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-5 and 8 stand and newly added claims 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants summarize the basis of the rejection and acknowledge the teachings in the cited references depicting the complexity of cellular re-programing. However, Applicants argue that the working example demonstrating that practicing the described method can result in a cell which expresses a stem cell marker (bottom of page 3). Applicants note that the claims have been amended to encompass the working example provided in the instant specification, and clearly indicate that the resulting cell expresses telomerase, a gene product known to be associated with a stem cell (top of page 4). Applicants' summarize the results provided in working Example 2, and argue that one of skill in the art would reasonably expect that somatic cells treated by the claimed methods would result in pluripotential stem cell (bridging pages 4-5). See Applicants' amendment pages 3-5. Applicants' arguments have been fully considered but not found persuasive.

Examiner acknowledges the amendments to the claims and the results presented in the working examples. However, even in light of narrowing of claim language by reciting the specific method steps the claims are still broadly drawn to reprogramming any human somatic cell into a pluripotent stem cell by administering to said somatic cell an agent which promotes cellular reprogramming. Again, the basis of the instant invention focuses on the ability to modify

any somatic cell and erase the changes which occur during differentiation, methylation patterns of the genome and acetylation of histones to restore the genome of a differentiated cell to a state which represents an undifferentiated stem cell.

Applicants' arguments that the claims have been amended to be commensurate in scope with the working examples is not persuasive because the claims encompass any somatic cell, and various agents described only functionally in the method steps. Even combining all the limitations of the dependent claims as it would describe the working example, there is no evidence that the resulting cell is a pluripotent stem cell. The agents specifically recited in the claims are known in the art and have been used extensively for studying specific effects of methylation and acetylation on gene regulation. As acknowledged in Applicants response, in the instant specification and as set forth in the previous office action, the art teaches that gene activation/deactivation during differentiation is a very complex process and determined by many factors. The work of Kikyo *et al.*, Walsh *et al.* and Keohane *et al.* provides evidence that simply providing agents known to alter the chromosomes in a cell will result in observable phenotypic changes in a cell, however these phenotypic changes are specific to the cell which is treated and to the compound used. Each Kikyo *et al.* and Walsh *et al.* summarize the art and their results indicating that the simplistic approach to nuclear reprogramming is not well supported. Kikyo *et al.* teach that the only method known in the art for returning a nucleus of a somatic cell to a more pluripotent state is the use of nuclear transfer, the transfer of a somatic nucleus into an enucleated oocyte. In this case, the factors provided by the oocyte are unknown and would not be

represented by the specific functional agents recited in the claims. Walsh *et al.* provides a review of the nature of differentiation as it is related to methylation of several genes known to alter expression in a tissue specific pattern, however while this pattern is recapitulated by the cell during normal differentiation, the *in vitro* evidence makes the methylation-development hypothesis ambiguous. Walsh *et al.* conclude based on previous results in the art and on their new evidence that methylation plays only a minor role in mammalian development, and that methylation is a consequence rather than a cause of transcriptional regulation. Similarly, Keohane *et al.*, Eickhoff *et al.* and Hou *et al.* provide clear evidence that the agents used in the instantly claimed method clearly affect gene expression, however the changes in expression are not predictable or representative of a cell which is de-differentiated. The art as a whole teaches that reprogramming a cell is a complex process and the evidence that the specific agents contemplated in the instantly claimed method clearly do not result in a pluripotent cell. The amended claims are broad encompassing the use of agents described only by function. Even in the specific embodiments of the agents in the dependent claims, based on the observations of others in the art for use of the agents in other cell types there is no evidence that an observed phenotype represents any clear or specific cell type. Clearly the agents affect gene expression, however there is no indication that the gene expression correlates with a specific cell type or cell status.

Applicants argue that the working example provides evidence that the claimed invention is more than a germ of an idea is not found convincing because there is no clear nexus between

the complexity of reprogramming a cell as taught in the art and acknowledged by Applicants and the single working example using specific agents and describing changes in expression of only a few genes. 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable". In this case, the art teaches that hypothesis on which the instant invention is based is not well founded, and proven not be a simple extension of cause and affect when modifying the chromosome of a cell to re-program a cell. The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005). The specification provides insufficient guidance to practice the method as instantly claimed. Without the necessary guidance in the specification and the lack of correlative working examples, the claims would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed, and the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-5, 8, 21 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

First, each of the previous specific rejections have been obviated by the amendments to the claims.

Newly amended claim 1 is unclear in the recitation of "a pluripotent stem cell which expresses a telomerase gene product" because the relationship of telomerase expression to practicing the method and its relationship to a resulting cell is not clearly set forth. Initially it is noted that a cell which has telomerase activity does not define a pluripotent stem cell, and cells such as transformed and immortalized cells, *in vivo* and in culture, demonstrate teleomerase activity. Additionally, it is noted that the art teaches that pluripotent stem cells have telomerase activity, and this embodiment would be only descriptive of a pluripotential stem cell. With respect to claim 1, it is unclear if telomerase expression is the only embodiment of the resulting cell or why this embodiment of a stem cell is recited to describe the pluripotential stem cell since these cells have telomerase activity. Applicants have indicated that the claims have been amended to be consistent with the examples provided in the specification, however while it noted that telomerase activity was assayed in the working examples, this activity alone is not indicative

of a pluripotent cell. The claims are unclear because the metes and bounds of the claim are indefinite because what cell is specifically obtained is confusing. It is not clear if the method results in a pluripotent stem cell comprising all the characteristics of this cell type known in the art, or does the claim encompass a cell in which telomerase activity is present. Dependent claims are included in the basis of the rejection because they fail to clarify the specific cell which is being generated, describing only specific agents used in the method. More clearly indicating what type of resulting cell is obtained from practicing the method would obviate the basis of the rejection.

Claims 4 is vague and unclear because what each of the specific agents represent is not clearly set forth. It is not clear if these agents represent one tow or three of the agents specifically indicated in claim 1, or they represent additional agents subsequently added.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3 and 4 rejected under 35 U.S.C. 102(b) as being anticipated by Yoshihiko *et al.* (1999, IDS reference BB) is withdrawn.

Applicants note the amendment to claim 1, and argue that the teaching of Yoshihiko *et al.* does not anticipate the claims as amended. See Applicants' amendment, page 6. Applicants' arguments have been fully considered and found persuasive.

Specifically, the claim amendments to encompass the administration of multiple agents has differentiated the claimed invention from that taught by Yoshihiko *et al.*

Conclusion

No claim is allowed. The claims are free of the art of record because the art does not specifically teach to treat keratinocytes with the agents recited by the claims, however they are subject to other rejections.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however,

will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800/1630